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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/613,097	07/01/2003	Robert T. Lyons	17550 (AP)	5104

7590 12/28/2004

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EXAMINER
FEDOWITZ, MATTHEW L

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,097	LYONS ET AL.	
	Examiner	Art Unit	
	Matthew L. Fedowitz	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☒ Claim(s) *3,4,20,24,25,37,38,42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/5/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-46 are pending in this application.

Claim Objections

Claims 3, 4, 20, 24, 25, 37, 38, 42 and 43 objected to because of the following informalities:

I. Claim 24 inadvertently refers to claim 24 when it should properly refer to claim 23.

II. Claims 3, 4, 37, 38 and 42 and 43 are duplicate claims. These compounds have the same chemical structure and only differ in their synthesis where one is synthetic and the other is naturally occurring.

III. Claim 25 does not end with a period. All claims must end with a period (see MPEP 608.01(m)).

IV. Claim 20 uses the phrase "viscosity agent." This phrase is not defined in the specification and will be interpreted as meaning a viscosity-increasing agent as in claim 19. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention,

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "tolerable threshold" in claim 1 is indefinite and not defined in the

specification. This phrase has many different definitions and there are no means of determining what a "tolerable threshold" may be.

Claims 2-5 and 29-31 are also rejected because claims that depend from an indefinite claim are also indefinite. See Ex parte Cordova, 10 USPQ2d 1949 (Bd. Pat. App. & Inter. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh *et al.* (US 2003/0232089 A1), Ikari *et al.* (US 6,232,343 B1), Hellberg *et al.* (US 6,646,001 B2), Olejnik *et al.* (US 6,562,873 B2), Su *et al.* (US 6,828,356 B2), the USP, Martin *et al.* and Gennaro *et al.*

I. Claim 1 is directed to a method of reducing an irritating or adverse effect associated with topical ophthalmic drugs that incorporate cyclodextrin to complex the drug such that the concentration of free active drug is reduced below a tolerable threshold, incorporating an effective amount of a viscosity increasing agent so the bioavailability is high enough to be therapeutically effective and cyclodextrin is not required to solubilized or stabilize the active drug. Claim 2 narrows claim 1 to the drug being a prostaglandin. Claim 3 narrows claim 1 to the active drug being prostamide. Claim 3 narrows claim 1 to the drug being bimatoprost. Claim 5 narrows claim 1 to the irritating side effect being hyperemia. Claim 29 narrows claim 1 to the active drug being between 8% and 90% of the active drug. Claim 30 narrows claim 1 to the free active drug being between 8% and 75% of the active drug. Claim 31 narrows claim 1 to the active drug to between 8% and 25% of the active drug.

Ikari *et al*. teach a method of adding cyclodextrin to prostaglandin drug formulations to reduce irritating side effects such as hyperemia (see column 4 lines 5-16). Ikari *et al*. does not teach the addition of a viscosity increasing agent; that cyclodextrin is not necessary to solubilized the drug; the use of prostamide or bimatoprost or that the amount of free active drug from the active drug.

As relating to claim 1, the addition of the viscosity-increasing agent in the method is suggested in Singh *et al*. (see paragraph 5) as well as in Hellberg *et al*. (see column 8 lines 59-67 and column 9 lines 1-5). As relating to claim 2, the use of a prostaglandin is suggested in Hellberg *et al*. (see claim 1). As relating to claims 3 and 4, Hellberg *et al*. also suggests the use of bimatoprost (see claim 3) and since bimatoprost is only a synthetic analog of prostamide they will be considered to be equivalent (see USP bimatoprost monograph on page 119-120). As

relating to claims 29-31, Gennaro *et al.* suggest that with cyclodextrin drug complexes, the complex stability and binding kinetics will inherently allow for free drug to exist when drug complexes exist regardless of how much cyclodextrin is added. Therefore, free drug will always exist when complexes form between cyclodextrin and prostaglandin or derivatives thereof (see page Gennaro *et al.* page 117 second column fifth full paragraph third sentence (above figure 9)). Moreover, it would be obvious to one skilled in the art to optimize such formulations as the applicant has done with claims 29-31.

Singh *et al.* provide the motivation to claim a method of inhibition of irritating side effects associated with the use of topical ophthalmic medications because a major problem encountered with ophthalmic drugs is their topical delivery (see paragraph 3) and that by prolonging the drug residence time in the eye drug absorption can be maximized (see paragraph 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to claim a method of inhibition of irritating side effects associated with the use of topical ophthalmic medications having the above-cited references before him. By considering all the prior art cited it would lead one skilled in the art to have a reasonable expectation of success in combining Singh *et al.* (US 2003/0232089 A1), Ikari *et al.* (US 6,232,343 B1), Hellberg *et al.* (US 6,646,001 B2), the USP and Gennaro *et al.* to produce the method claimed.

II. Claim 35 is directed a method of reducing a side effect associated with a drug administered topically to a patient's eye by providing a solution of drug in a therapeutically

effective amount that causes a side effect, then complexing a portion of the drug with cyclodextrin to lower the concentration of the drug causing the side effect and then incorporating a viscosity increasing agent to increase the contact time to more effectively deliver the drug. Claim 36 narrows claim 35 to the active drug being prostaglandin. Claim 37 narrows claim 35 to the active drug being prostamide. Claim 38 narrows claim 35 to the active drug being bimatoprost. Claim 39 narrows claim 35 to the side effect being hyperemia.

The teachings of Ikari *et al.* are discussed above. Ikari *et al.* does not teach the addition of a viscosity increasing agent; the use of prostamide or bimatoprost or that the amount of free active drug from the active drug or that the drug is released over time at a rate insufficient to cause side effects.

As relating to claims 35-39, the teachings of Ikari *et al.* are discussed above as well as the teachings of Hellberg *et al.* and the USP. Also relating to claim 35, Martin *et al.* teach that cyclodextrins are useful as sustained release drug carriers (see p. 260 second column first and second full paragraphs) thereby releasing the drug at such a rate as to not cause side effects.

Singh *et al.* provide the motivation to claim a method of inhibition of irritating side effects associated with the use of topical ophthalmic medications because a major problem encountered with ophthalmic drugs is their topical delivery (see paragraph 3) and that by prolonging the drug residence time in the eye drug absorption can be maximized (see paragraph 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to claim a method of inhibition of irritating side effects associated with the use of topical ophthalmic medications having the above-cited references before him. By

considering all the prior art cited it would lead one skilled in the art to have a reasonable expectation of success in combining Ikari *et al.* (US 6,232,343 B1), Hellberg *et al.* (US 6,646,001 B2), the USP and Martin *et al.* to produce the method claimed.

III. Claim 6 is directed to a topical ophthalmic formulation that contains an active drug , cyclodextrin in an amount to lower the amount of free active drug that causes adverse side effects as well as a viscosity-increasing agent. Claim 23 narrows claim 6 by the concentration of bimatoprost being 0.03%, 0.6% boric acid, about 0.045%borate, about 0.34%sodium chloride, about 0.14% potassium chloride and about 0.01% Purite®. Claim 24 narrows claim 23 to where the viscosity-enhancing agent is carboxymethylcellulose at a concentration of about 1%. Claim 28 narrows claim 24 to where the cyclodextrin is 2-hydroxypropyl γ-cyclodextrin at a concentration of about 0.5%. Claim 46 narrows claim 24 to where the cyclodextrin is γcyclodextrin in a concentration of about 0.21%. Claim 25 narrows claim 24 to where the cyclodextrin is sodium hydroxypropyl β-cyclodextrin at a concentration of about 0.05% to about 1.1%. Claim 26 narrows claim 25 to where the concentration of 2-hydroxypropyl β-cyclodextrin is about 1%. Claim 27 narrows claim 25 to where the concentration of 2-hydroxypropyl β-cyclodextrin is about 0.08%. Claim 45 narrows claim 6 to where the active drug is a prostaglandin. Claim 8 narrows claim 6 to include a buffer to maintian the pH at about 7.3, one or more tonicity agents and a preservative. Claim 9 narrows claim 8 to where the buffer is borate and the preservative is Purite®. Claim 7 narrows claim 6 to where the ophthalmic formulation is bimatoprost. Claims 10 and 11 narrow claim 7 to where the concentration of bimatoprost is between about 0.003% and 0.1% and 0.01% and about 0.05%, respectively. Claims 12 and 13

narrows claim 7 to where the concentration of bimatoprost is about 0.03% and 0.02%, respectively. Claim 14 narrows claim 7 to where the cyclodextrin is 2-hydroxypropyl β-cyclodextrin, 2-hydroxypropyl γ-cyclodextrin, or γ-cyclodextrin. Claims 15, 16 and 17 narrows claim 7 to where the concentration of cyclodextrin is between about 0.01% and about 10%; about 0.05% and about 5% and 0.1% and about 1.1%, respectively. Claim 18 narrows claim 7 to where the viscosity of the formulation is about 30 centipoise and about 100 centipoise. Claims 19 and 20 narrow claim 7 to where the concentration of the viscosity-increasing agent is between about 0.1% and about 3% or about 1%, respectively. Claims 21 and 22 limit the viscosity agent to carboxymethylcellulose or hydroxypropylmethylcellulose. Claims 32, 33 and 34 narrow claim 7 to where the free active drug is between about 8% and 90%, 75% and 25% , respectively, of the active drug.

As relating to claims 6, 7, 10-14, 32-34 and 45-46 the teachings of Ikari *et al.*, Hellberg *et al.*, Gennaro *et al.* and Singh *et al.* are discussed above. Ikari *et al.* also teaches the concentration of prostaglandin being between 0.0001 to 1.0% weight (see column 4 lines 25-45) as the applicant has in claims 10-12 and the concentration of cyclodextrin and its derivatives (see column 4 lines 36-45) as the applicant has in claims 15-17 and 25-28.

That which Ikari *et al.* does not teach is discussed above. In addition, Ikari *et al.* does not teach the use of a buffer; a tonicity agent; a preservative; specific preservatives such as purite®; the amount of free bimatoprost; the viscosity of the formulation being between 30-100 centipoise; the concentration of the viscosity increasing agent; the type of viscosity increasing agent; the concentrations of bimatoprost, boric acid, sodium borate, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, purite® or carboxymethylcellulose.

As relating to claims 8, 9, and 19-24, Singh *et al.* teach that the use of a buffer to maintain pH in a ophthalmically acceptable range (see paragraph 94); the use of a tonicity agent and a preservative (see paragraph 59); the use of borate (see paragraph 93); the concentrations of a viscosity increasing agents (see paragraph 85) from which one skilled in the art would optimize such formulations; and the concentrations boric acid, sodium borate, sodium chloride, potassium chloride, calcium chloride and magnesium chloride (see paragraphs 93 and 94) from which one skilled in the art would optimize such formulations. As relating to claims 9 and 23, Olejnik et al. teach the use of purite® as a preservative (see column 11 lines 28-30) from which one skilled in the art would optimize such a formulation. As relating to claim 18, Su *et al.* teach an optimized viscosity for ophthalmic formulations between 20 and 150 centipoise in the same manner as the applicant has claimed (see column 1 lines 66-67). As relating to claim 23, Hellberg *et al.* teach that bimatoprost is a prostaglandin analog used in ophthalmic formulations (see claim 3) and, as such, one skilled in the art would know to use it as a the prostaglandin as suggested in the formulations of Singh *et al.*

Singh et al. provide the motivation to claim a topical ophthalmic formulation capable of inhibiting the irritating side effects associated with the use of topical ophthalmic medications because a major problem encountered with ophthalmic drugs is their topical delivery (see paragraph 3) and that by prolonging the drug residence time in the eye drug absorption can be maximized (see paragraph 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to claim a topical ophthalmic formulation capable of inhibiting the irritating side effects associated with the use of topical ophthalmic medications having the above-cited

references before him. By considering all the prior art cited it would lead one skilled in the art to have a reasonable expectation of success in combining Sing *et al.* (US 2003/0232089 A1), Ikari *et al.* (US 6,232,343 B1), Hellberg *et al.* (US 6,646,001 B2), Olejnik *et al.* (US 6,562,873 B2), Su *et al.* (US 6,828,356 B2), the USP, Martin *et al.* and Gennaro *et al.* to produce the formulation claimed.

IV. Claim 40 is directed to a topical formulation prepared by a process of providing the a solution of stable and soluble drug that causes a side effect then complexing the drug in a solution with cyclodextrin to lower the free active concentration of the drug and then incorporating a viscosity increasing agent to increase the contact time with the eye. Claims 41-43 narrow claim 40 to where the drug is prostaglandin, prostamide or bimatoprost, respectively. Claim 44 narrows claim 40 to where the side effect is hyperemia.

As relating to claims 40-44 the teachings of Ikari *et al.*, Hellberg *et al.*, Gennaro *et al.* and Singh *et al.* are discussed above. That which Ikari *et al.* does not teach is also discussed above.

Singh *et al.* provide the motivation to claim a topical ophthalmic formulation capable of inhibiting the irritating side effects associated with the use of topical ophthalmic medications because a major problem encountered with ophthalmic drugs is their topical delivery (see paragraph 3) and that by prolonging the drug residence time in the eye drug absorption can be maximized (see paragraph 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to claim a topical ophthalmic formulation capable of inhibiting the irritating side effects associated with the use of topical ophthalmic medications having the above-cited

references before him. By considering all the prior art cited it would lead one skilled in the art to have a reasonable expectation of success in combining Singh *et al.* (US 2003/0232089 A1), Ikari *et al.* (US 6,232,343 B1), Hellberg *et al.* (US 6,646,001 B2), the USP, and Gennaro *et al.* to produce the formulation claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Matthew L. Fedowitz whose telephone number is (571) 272-3105 and can be reached between 9am-5:30pm (EST) M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Mr. James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew L. Fedowitz, Pharm.D., J.D.
December 6, 2004

James O. Wilson
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Art Unit 1623